B120

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 January 2006 (26.01.2006)

PCT

(10) International Publication Number
WO 2006/007676 A1

(51) International Patent Classification[7]: A61K 35/78, A61P 31/18

(21) International Application Number: PCT/BR2004/000127

(22) International Filing Date: 21 July 2004 (21.07.2004)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/007676 A1

(54) Title: COMBINATION OF ACTIVE FRACTIONS FROM THE PLANTS *EUPHORBIA TIRUCALLI L* AND *FICOS CARICA L.* AND METHOD OF TREATING CANCER AND AIDS

(57) Abstract: The present invention refers to the combination of active fractions from the plants *Euphorbia tirucalli L.* e *Ficus carica L.* more particularly the pharmaceutical compositions comprising the said combinations, which are useful for treatment of cancer and Acquired Immunodeficiency Syndrome (AIDS). The present invention also relates to the process of manufacture of the active fractions from the plants.

"COMBINATION OF ACTIVE FRACTIONS FROM THE PLANTS *EUPHORBIA TIRUCALLI L.* AND *FICUS CARICA L.* AND METHOD OF TREATING CANCER AND AIDS"

FIELD OF THE INVENTION

The present invention refers to the combination of active fractions from the plants *Euphorbia tirucalli L.* e *Ficus carica L.*, more particularly the pharmaceutical compositions comprising the said combinations, which are useful for treatment of cancer and Acquired Immunodeficiency Syndrome (AIDS). The present invention also relates to the process of manufacture of the active fractions from the plants.

BACKGROUND OF THE INVENTION

Since the sprouting of the AIDS and the cancer the constant development of new methods of treatment and new drugs comes significantly drawing out the life of the patients for difficult the evolution of both illnesses.

The medicaments used in the treatment of the AIDS postpone the beginning of the illness decelerating the rhythm of the reduction of the cells CD4. But, still thus, they are incapable to cure the illness. Four main types of drugs exist, that act in different phases of the illness: entrance inhibitors, reverse transcriptase nucleosides and non-nucleosides inhibitors and protease inhibitors. Some of these medicines must be managed of agreed form. Generally at least three drugs of two different categories are used simultaneously.

In the same way, many searches are being carried out for the development of new treatments for cancer. The conventional treatments include surgery, radiotherapy, chemotherapy and some drugs administration.

However, the available treatments for AIDS or Cancer therapy provide accented collateral effects to the patients, either of clinical nature, such as nausea, vomit, headache, fatigue, spots in the skin, sleeplessness, stomach

ache, muscular problems in the liver, pancreas and nerves, wounds in the mouth, inflammation, anemia, pains and weakness, or of psychological nature, such as the physical mutilation with the withdrawal organs, or with the fall of hair when the utilization of radiotherapy and/or chemotherapy.

Thus, it is desired the development of new therapies that do not provide the collaterals effects described above.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the combination of active fractions from the plants *Euphorbia turicalli L.* and *Ficus carica L.*, useful for treating cancer and AIDS, which not causes physicals and/or psychological damages to patients.

The *Euphorbia turicalli L.* is a member of the *Euphorbiaceae* family, native from Oriental Africa and Asia, also known as "aveloz", "esqueleto", "graveto de cão", "dedo do diabo", "espinho italiano" São Sebastião tree, petroleum plant, milkbush, pencil tree, finger tree, Indian tree spurge, milkhedge, rubber euphorbia, euphorbe antivenerien, among other. The plant includes the following chemical compounds: 12-o-(2Z)(4E)-octadienol-4-deoxyphorbol-13-acetate, 3,3'-di-o-methylellagic-acid, beta-sitosterol, citric acid, ellagic acid, euphol, euphorone, glucose, hentriacontane, hentriacontanol, isoeuphoral, kamepferol, malic acid, resin, sapogenine acetate, succinic acid, taraxasterol, taraxerin and tirucallol.

The latex obtained from the plant *Euphorbia tirucalli L.* is toxic, irritant and caustic. The sap milky can cause lesion and edema on skin and mucous, irritation, eyes tearingly, edema of eyelids and even though vision difficult. The latex ingestion may also cause nausea, vomits, diahea and some amounts can be fatal.

Ficus carica L. is a member of the *Moraceae* family, native from Asia (Mediterranean region), also called fig and "figo roxo". The plant includes

the following chemical compounds: araquidic acid, ascorbic acid, boric acid, citric acid, fumaric acid, glutamic acid, linoleic acid, linolenic acid, malic acid, oleic acid, oxalic acid, pantothenic acid, quinic acid, succinic acid, arabinose, arginine, carbohydrates, beta-carotene, chlorophyll cystin, fitosterols, fructose, glycine, glucose, histidine, isoleucine, leucine, lutein, mucilage, pectin, protein, riboflavin, mineral salts (boron, calcium, copper, phosphorus, potassium and zinc), serine, sucrose, valine, vitamin B6 and the leafs contain furanocumarines.

Process for the manufacture of the active fractions from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* according to the invention comprise the steps:

a) dissolution of the latex obtained from *Euphorbia tirucalli L.* in water until the concentrations of about 1 ppm to about 10,000 ppm at neutral pH;

b) decoction of the leafs from *Ficus carica L.* in water until the concentrations of about 0.1 to about 10%, preferably about 2,5%, inducing and keeping the heating until the temperature of about 70 to 100°C for about 20 to 30 minutes and after cooling by a natural or induced process;

c) filtering the product of b) to remove the impurities or solid residues;

d) dissolution of the product of c) until concentrations of about 20% to about 40%, preferably about 30% at little acid pH; and

e) mixing the active fraction obtained in a) and d) steps.

The active fractions obtained by (1) and (2) are combined in ratio ranges varying from about 2:1 to about 2:100 or from about 2:1 to about 100:1 respectively and should comprise pH limits varying from about 2 for the concentrated product to about 7 for the diluted product.

The active fractions combined according to the invention are useful in the treatment of Cancer and AIDS and present analgesic activity, antioxidant, anti-inflammatory, anti rheumatic, emetic, immunessupressor, rubefacient, hipoglicemiant, expectorant, digestive and depurative. Moreover, it

can be used internally against scorpions and snakes bites and externally in warts, rheumatic ache, physical damages, asthma, cough, and insects repellent.

Moreover, the combination of active fractions according to the invention does not present adverse effects of the plant *Euphorbia tirucalli L.*. The combined product also provides the acceleration of the treatment process if compared to the traditional treatments.

The present invention also describes pharmaceutical compositions comprising at least one of the active fractions of the plants *Euphorbia tirucalli L.* and *Ficus carica L.* or their combination together with pharmaceutical acceptable carriers.

The pharmaceutical compositions according to the present invention may contain about 0.001% to about 5% by weight of the active fraction from *Euphorbia tirucalli L.* and about 0.001% to about 50% by weight of the active fraction of *Ficus carica L.*.

The compositions according the present invention may be administered by orally (immediate or sustained release forms), parenterally (intramuscular, endovenous, intraarteral, intraperitoneal, intrathecal, subcutaneous, hypodermic or intradermic forms), mucosally (pulmonary, sublingual, nasal, conjuctival, rectal or vaginal formsmucosally) or topically.

The appropriated forms includes all the forms known in the art, such as solutions, suryps, suspension, emulsion, lotion, cream, gel, aerosol, tablet, capsule, pellets and other.

The pharmaceutical acceptable carriers according to the invention may include all known in the art, such as lactose, glucose, methyl cellulose, magnesium stearare, dicalcium phosphate, calcium sulphate, manitol, sorbitol, ethanol, glycerol, water and similar.

The composition according to the invention may include as

necessary one or more pharmaceutical additives, such as agglutinants, lubrificants, desintegrants agents, color agents and other.

The present invention refers to the use of the combination of active fractions in the manufacture of a medicament or pharmaceutical composition useful in treatment of cancer or AIDS.

The present invention also refers to the method of treating cancer and AIDS by the administration of the combination of active fractions from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* or the administration of the pharmaceutical compositon comprising said active fractions mentioned above.

The following example illustrates a particular embodiment of the invention without any limitation.

EXAMPLES

The active fraction of *Euphorbia tirucalli L.* was gotten becoming fluid 0,5ml of the latex extracted of the plant in 1 liter of water (concentration of the solution 436,35ppm, or either, 0,43635g of the latex for one 1 kg of solution). pH measured in the diluted product was 7,12.

The active fraction of *Ficus carica L.* was prepared weighing initially 25g of leves of the related plant, placing them on decoction in 1 liter of water until the temperature of 70°C and remaining superior temperature 70°C for about 25 minutes (maximum temperature reached 98-100°C). After that the gotten cool and filtered product. The gotten intent product then was diluted with water 30% (300 mL of product concentrated for 1 liter of water). pH measured in the diluted product was of 5,43.

The gotten fractions later had been combined.

CLAIMS

1. Combination of active fractions from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* comprising at least the 12-o-(2Z)(4E)-octadienol-4-deoxyphorbol-13-acetate, 3,3'-di-o-methylellagic-acid, beta-sitosterol, citric acid, ellagic acid, euphol, euphorone, glucose, hentriacontane, hentriacontanol, isoeuphoral, kamepferol, malic acid, resin, sapogenine acetate, succinic acid, taraxasterol, taraxerin, tirucallol into the active fraction of *Euphorbia tirucalli L.* and at least the araquidic acid, ascorbic acid, boric acid, citric acid, fumaric acid, glutamic acid, linoleic acid, linolenic acid, malic acid, oleic acid, oxalic acid, pantothenic acid, quinic acid, succinic acid, arabinose, arginine, carbohydrates, beta-carotene, chlorophyll cystin, fitosterols, fructose, glycine, glucose, histidine, isoleucine, leucine, lutein, mucilage, pectin, protein, riboflavin, mineral salts (boron, calcium, copper, phosphorus, potassium and zinc), serine, sucrose, valine, vitamin B6 and furanocumarines into the active fraction of *Ficus carica L.*

2. Combination according to claim 1 comprising active fractions of *Euphorbia tirucalli L. and Ficus Carica L* in ratio ranges varying from about 2:1 to about 2:100 or from about 2:1 to about 100:1.

3. Combination according to claims 1 to 2 wherein the pH varies from about 2 to about 7.

4. Use of the combination as defined in claims 1 to 3 in the manufacture of a medicament useful in treatment of cancer or AIDS.

5. Pharmaceutical composition comprising the combination of active fractions from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* together with at least a pharmaceutical acceptable carrier.

6. Pharmaceutical composition according to claim 5 comprising from about 0,001 % to about 5 % by weight of an active fraction from *Euphorbia tirucalli L.* and from about 0,001 % to about 50 % by weight of an active fraction

from *Ficus carica L.*

7. Pharmaceutical composition according to claims 5 to 6 wherein said composition is intended to be administered orally, parenterally, mucosally or topically.

8. Pharmaceutical composition according to claim 7 wherein the said composition is intended to be administered orally by immediate or sustained release forms.

9. Pharmaceutical composition according to claim 7 wherein the said composition is intended to be administered parenterally by intramuscular, endovenous, intraarteral, intraperitoneal, intrathecal, subcutaneous, hypodermic or intradermic forms.

10. Pharmaceutical composition according to claim 7 wherein the said composition is intended to be administered mucosally by pulmonary, sublingual, nasal, conjuctival, rectal or vaginal forms.

11. Use of the pharmaceutical composition as defined in claims 5 to 10 in the manufacture of a medicament useful in treatment of cancer or AIDS.

12. Process for the preparation of active fraction from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* comprising the steps:

a) dissolution of the latex obtained from *Euphorbia tirucalli L.* in water until the concentrations of about 1 ppm to about 10,000 ppm at neutral pH;

b) decoction of the leafs from *Ficus carica L.* in water until the concentrations of about 0.1 to about 10%, preferably about 2,5%, inducing and keeping the heating until the temperature of about 70 to 100°C for about 20 to 30 minutes and after cooling by a natural or induced process;

c) filtering the product of b) to remove the impurities or solid residues;

d) dissolution of the product of c) until concentrations of about 20% to about 40%, preferably about 30% at little acid pH; and

e) mixing the active fraction obtained in a) and d) steps.

13. Method of treating cancer and AIDS comprising the administration of the combination of active fractions from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* as defined in claims 1 to 3.

14. Method of treating cancer and AIDS comprising the administration of the pharmaceutical composition including the combination of active fractions from the plants *Euphorbia tirucalli L.* and *Ficus carica L.* as defined in claims 5 to 10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BR 2004/000127

A. CLASSIFICATION OF SUBJECT MATTER
IPC[7]: A61K 35/78, A61P 31/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[7]: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, EPODOC, internet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BR 2002022733 A (AMAZONIA FITOMEDICAMENTOS LTDA) 11 May 2004 (11.05.2004) *the whole document*	1, 2, 4-6, 11-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2005 (15.03.2005)	7 June 2005 (07.06.2005)

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International application No.
PCT/BR 2004/000127

INTERNATIONAL SEARCH REPORT

Continuation of first sheet

Continuaton No. II

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 13,14 because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 and 14 are directed to a therapeutic method of treatment of the human/animal body, the search has been carried out and is based on the alleged effects of the composition.

Claims Nos.: 3, 7-10 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 3 is function-orientated, because it does not disclose how the pH is achieved. The characterisation of a pharmaceutical composition (claims 7-10) by its way of administration is not allowed.